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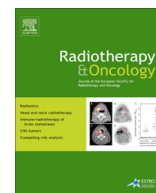
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## Original article

# Functional Swallowing Units (FSUs) as organs-at-risk for radiotherapy. PART 1: Physiology and anatomy



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## ABSTRACT

**Background and purpose:** When optimising radiotherapy treatments today, the pharyngeal constrictor muscles and the larynx are usually regarded as the swallowing organs at risk (SWOARs). The purpose of this study was to identify and describe additional, previously undefined groups of muscles (functional units) involved in crucial components of swallowing (hyolaryngeal elevation (HLE), tongue base retraction (TBR) and tongue motion), and to emphasise their relevance in radiation-induced dysphagia. **Material and methods:** Based on available literature on human anatomy and swallowing physiology, the functional units of muscles involved in HLE, TBR and tongue motion have been identified and described.

**Results and conclusion:** Functional swallowing units (FSUs) were defined as groups of swallowing muscles sharing their function, that are in close proximity to each other. Seven FSUs involved in HLE, TBR and tongue motion were identified: floor of mouth, thyrohyoid muscles, posterior digastric/stylohyoid muscles complex, longitudinal pharyngeal muscles, hyoglossus/styloglossus muscles complex, genioglossus muscles, intrinsic tongue muscles. The swallowing physiology and anatomy of the FSUs described in this paper will lead to a greater understanding of radiation-induced dysphagia mechanisms and, consequently, to an improvement in the development of swallowing sparing strategies. This article (PART 1) serves as the theoretical foundation for a subsequent article (PART 2), which provides detailed delineation guidelines for FSUs.

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Swallowing disorders are common among patients undergoing definitive (chemo-) radiation for head and neck cancer even before treatment. The treatment may further deteriorate their swallowing function. To achieve better local control, treatment regimens have become more aggressive, resulting in higher rates of long-term dysphagia. Dysphagia has a negative impact on health-related quality of life (HRQL) and it is associated with a higher risk of malnutrition, tube feeding dependence and aspiration [1–3].

**Abbreviations:** SWOARs, Swallowing Organs At Risk; HLE, Hyolaryngeal Elevation; TBR, Tongue Base Retraction; FSUs, Functional Swallowing Units; FOM, Floor of Mouth; THM, Thyrohyoid Muscles; PDS, Posterior Digastric/Stylohyoid Muscles Complex; LPM, Longitudinal Pharyngeal Muscles; HSG, Hyoglossus/Styloglossus Muscles Complex; GGS, Genioglossus Muscles Complex; ITM, Intrinsic Tongue Muscles; NTCP, Normal Tissue Complication Probability.

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Aspiration, quite often of a silent nature, yields a high risk of potentially life threatening aspiration pneumonia [4–10]. Considering the clinical and social relevance of swallowing problems, many radiation oncologists introduced swallowing sparing strategies, using Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) [11–13]. To preserve swallowing function and increase consistency of published results, a consensus on the definition of swallowing organs at risk (SWOARs) has been established [14,15]. Typical SWOARs include the pharyngeal constrictor muscles, the larynx (both the glottic and supraglottic part), and the upper oesophageal sphincter. However, many questions related to the prevention of radiation-induced dysphagia have not been answered. It is not yet known whether any swallowing muscles other than these SWOARs may be neglected, whether active sparing of the SWOARs increases the dose distribution in other unidentified dysphagia structures, or whether other swallowing structures become more important if reduction of the dose to the consensus SWAORs is successful.

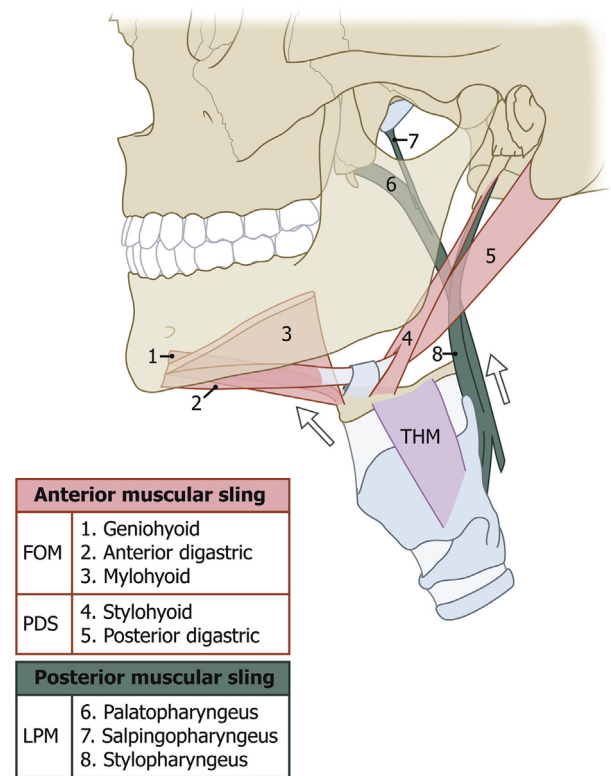
## General method

Hyolaryngeal elevation (HLE), tongue base retraction (TBR) and tongue motion are important components of swallowing and therefore may be relevant for radiation-induced dysphagia. Yet, none of the SWOAR-sparing concepts in common use today integrate these components in the definition of SWOARs and/or treatment planning objectives. In the following section, the physiology of these swallowing components and the muscles involved are described. Seven functional swallowing units (FSUs) were defined, including five groups of HLE/TBR muscles and two groups of tongue muscles, involved in tongue motion during the preparatory phase of swallowing. The tongue motion FSUs were considered relevant based on their potential impact on subjective swallowing complaints of radiotherapy patients. [16,17] Following their definition, a detailed description of the anatomy for each FSU is provided. This functional approach, based on the anatomy as well as on physiology, provides the theoretical basis for the delineation guidelines of FSUs, described in detail in a separate paper (PART 2).

## Swallowing physiology – selected aspects

Swallowing is a complex process, requiring perfect coordination of sophisticated volitional and reflexive actions to transfer airway into the digestive tube in less than a second. [18] During the voluntary oral preparatory phase, tongue motion supports a proper bolus preparation, guaranteed by the alternate contraction and relaxation of *intrinsic tongue muscles* and the *genioglossus muscles* – the latter being the largest and strongest extrinsic tongue muscles [19,20]. After the preparatory phase, the bolus is propelled posteriorly. It stimulates pharyngeal pressure receptors, which are mainly located at the base of the tongue and pharyngeal arches. This stimulation initiates the non-voluntary pharyngeal phase of swallowing [21]. The initiation of pharyngeal swallowing is marked by hyolaryngeal elevation (HLE) [22]. HLE is characterised by the up-and-forward movement of the hyoid bone and the larynx, which thickens the base of the epiglottis and provokes its tilting down, ensuring the closure of the laryngeal entrance. It also applies traction to the anterior wall of the pharynx, enabling the opening of the upper oesophageal sphincter and propulsion of the bolus from the pharynx into the oesophagus [21,23]. Biofeedback mechanisms are at least as important as the muscle power. Lack of even a small part of the swallowing movement may have an influence on subsequent parts of the swallowing process. HLE, critical for an efficient and safe swallowing action, is facilitated mainly by contraction of the *floor of mouth*, pulling the hyoid bone up (mylohyoid muscles) and forward (geniohyoid muscles) [18,24]. Pearson et al. presented the *two-sling theory of HLE*, where the floor of mouth, together with the *posterior belly of the digastric muscles* and the *stylohyoid muscles*, form the anterior muscle sling of the HLE apparatus [18]. (Fig. 1) The movement of the larynx is both- a passive following of the hyoid as well as an active motion of the larynx towards the hyoid. The latter is supported by contraction of the *thyrohyoid muscles* (located between the thyroid cartilage and hyoid bone) and, especially, by the *longitudinal pharyngeal muscles* [23,25,26]. The longitudinal pharyngeal muscles form the posterior muscle sling, facilitating the shortening of the pharynx and larynx elevation during HLE [18,27] (Fig. 1).

After triggering the pharyngeal swallowing phase, the base of the tongue assumes a ramp shape and directs the bolus into the pharynx [21]. When the tail of the masticated bolus reaches the level of base of the tongue, tongue base retraction (TBR) is initiated. This shape change and posterior movement of base of the tongue is facilitated by the contraction of two other extrinsic tongue muscles: *hyoglossus muscles*, *styloglossus muscles* and, indirectly,



**Fig. 1.** Two-sling theory of hyolaryngeal elevation (HLE), according to Pearson et al. [18] and Functional Swallowing Units (FSUs) concept. Anterior muscular sling (pink) includes two FSUs involved in HLE: floor of mouth (FOM) and posterior digastric/stylohyoid muscles complex (PDS); posterior muscular sling (green) includes the 3rd FSU involved in HLE: longitudinal pharyngeal muscles (LPM). White arrows indicate the directions of movements caused by: anterior sling (up-and-forward movement of hyoid and larynx), posterior sling (upward movement of the larynx towards the hyoid, additionally supported by the 4th FSU (purple): thyrohyoid muscle (THM)). Illustration made by Remko van Deijk.

*genioglossus muscle* [19,20,28]. The base of the tongue moves towards the posterior pharyngeal wall and needs to make complete contact to maintain sufficient pressure on the bolus tail. Subsequently, the contraction wave of the posterior pharyngeal wall continues progressively down the pharynx to the upper oesophageal sphincter, where the bolus propulsion is taken over by oesophageal peristalsis. Sufficient pressure built up during TBR also facilitates timely and optimal opening of the upper oesophageal sphincter [21,23,29].

A recent morphometric study showed that both TBR and HLE (especially the movement of the larynx towards the hyoid, supported by longitudinal muscles) underlie the epiglottic inversion [26]. Epiglottic inversion is crucial for an effective vestibular closure (the second level of laryngeal protection after glottic closure) and thus for a safe and effective swallowing action without penetration (material above the vocal folds) and aspiration (material below the vocal folds) [21,23,30,31]. In other words, fluent HLE and effective TBR facilitate closing the airways on time so that the bolus can be smoothly pushed further down before the airways open again. Therefore, all aforementioned muscles should be considered SWOARs. Interestingly, videofluoroscopy performed after (chemo)radiation very often demonstrates reduction of HLE and TBR. Other common swallowing disorders include (partly due to reduced HLE and TBR) reduction of upper oesophageal sphincter opening and residue in the vallecula or pyriform sinus, which all may lead to penetration and aspiration. Reduced contraction of

pharyngeal wall has also been observed, although it may be more challenging to capture [4,32–37]. It should also be noted that functional disorders of pharyngeal swallowing can be more easily identified than structural abnormalities of swallowing structures, which makes videofluoroscopy (together with the Fiberoptic Endoscopic Evaluation of Swallowing, FEES) the diagnostic gold standard [13,38,39].

### **Structure anatomy**

All muscles described below are divided into muscular groups, based on their shared function and close proximity, forming Functional Swallowing Units (FSUs).

#### **FSUs involved in hyolaryngeal elevation**

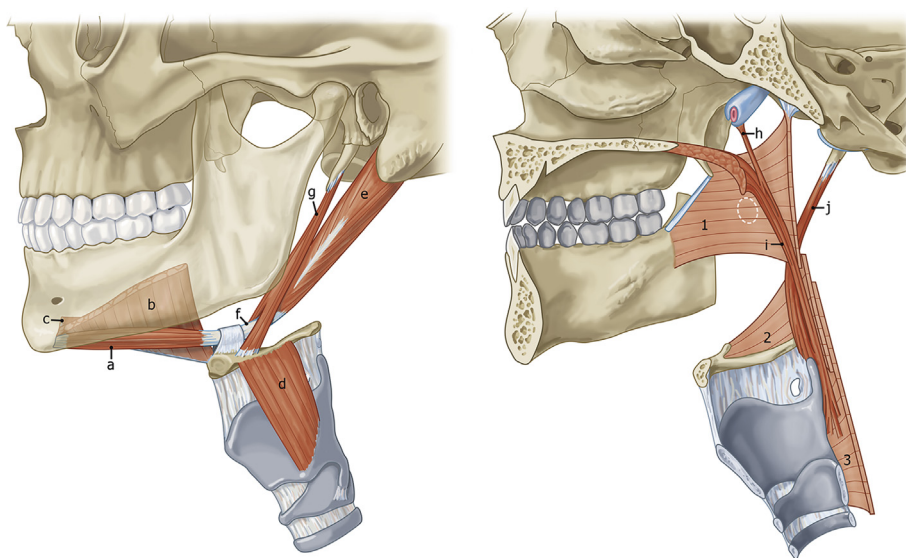
**The floor of mouth (FOM)** contains three twin muscles: the anterior belly of the digastric muscle, the mylohyoid muscle and the geniohyoid muscle. The *anterior digastric muscle* lies most caudally and runs from the inner part of the mandible (midline) to the intermediate tendon of the digastric muscle, attached to the hyoid bone (body and greater cornu) (Fig. 2a). The flat triangular *mylohyoid muscle* is situated right above the anterior digastric muscle and spreads between the inner anterolateral part of the mandible and (postero-medially) the anterior surface of the hyoid. Posterolaterally it forms a free edge (Fig. 2b; 3.1). The right and left mylohyoid muscles intermesh with each other along their medial edges (raphe) in the midline of the floor of mouth. Together, they form the oral cavity diaphragm (*diaphragma oris*) in the shape of a shallow bowl. The *geniohyoid muscle* is a narrow muscle situated immediately above the medial edge of the mylohyoid. It runs from the inner part of the mandible to the middle part of the hyoid bone. It lies immediately under the largest tongue muscle, i.e. the genioglossus (Fig. 2c; 3.2). The medial edge of geniohyoid muscle adjoins the medial edge of the opposite muscle [19,40].

**The thyrohyoid muscle (THM)** is a small and even muscle. It is the only infrahyoid muscle that facilitates the HLE. It arises from

the oblique line on the lamina of the thyroid cartilage and runs into the lower border of the greater cornu of the hyoid bone [19] (Fig. 2d). As it is located in the middle of the hyolaryngeal complex, the thyrohyoid muscles of both sides (forming one functional unit, THM) elevate the larynx towards the hyoid at the beginning of HLE and depress the hyoid at the end of it.

**The posterior digastric/stylohyoid muscles complex (PDS)** consists of the posterior belly of digastric muscle and the stylohyoid muscle. The *posterior belly of the digastric muscle* arises from the mastoid notch, a deep groove between the mastoid and the styloid process [19]. The posterior digastric runs anteriorly and downwards to become a tendon attached to the hyoid bone, just where the anterior belly ends (Fig. 2e). This tendon (*tendon intermediate*) connects two parts of the digastric muscle, which both take part in the hyoid bone elevation [19,20] (Fig. 2f). The *stylohyoid muscle* is more slender than the posterior digastric, situated close anteriorly and superiorly to it. It arises from the styloid process of the temporal bone and runs anteriorly and downwards, quickly joining the posterior digastric. It runs into the anterior surface of the hyoid bone and, at its insertion point, it is perforated by the tendon intermediate of the digastric muscle [19] (Fig. 2f,g). These two muscles share not only the course and insertion point, but also the innervation and their function, carrying the hyoid bone up- and backward at the end of the HLE. This helps prevent the return of the bolus into the mouth [19].

**The longitudinal pharyngeal muscles (LPM)** include three twin muscles of the upper part of the pharynx: the *salpingopharyngeal*, *palatopharyngeal* and *stylopharyngeal* muscles. The *salpingopharyngeal muscle* arises from the medial cartilage of the pharyngotympanic tube, forming the posterior edge of the torus tubarius [41]. It passes downwards and, approximately at the level of and behind the palatine tonsil, it joins and connects to the other longitudinal muscle, the *palatopharyngeal muscle* (Fig. 2h). *Palatopharyngeal* originates in the soft palate, laterally to the (centrally located) uvula. The two opposing palatopharyngeal muscles join each other through the midline of the soft palate. They run further downward and backward along the lateral side of the pharynx and, covered by the mucous membrane, they form the palatopharyngeal folds (posterior pillars of the pharynx), located posteriorly to the palatine



**Fig. 2.** Functional Swallowing Units involved in hyolaryngeal elevation (HLE), *sagittal lateral view*: a–c: floor of mouth (FOM): a– anterior belly of digastric muscle, b– mylohyoid muscle, c– geniohyoid muscle (from this perspective only the origin of this muscle is visible, as it is situated above the mylohyoids; for further visualisation see Fig. 3.2); d– thyrohyoid muscle (THM); e–g: posterior digastric/stylohyoid muscles complex (PDS): e– posterior belly of digastric muscle, f– tendon intermediate of digastric muscle, g– stylohyoid muscle. *Sagittal medial view*: h–j: longitudinal pharyngeal muscles (LPM) h– salpingopharyngeal muscle, i– palatopharyngeal muscle, j– stylopharyngeal muscle. For better orientation and visualisation of relationship with LPM also illustrated: pharyngeal constrictor muscles: 1–superior, 2–medius, 3–inferior; the site of pharyngeal tonsil (white dashed line ellipse). Illustration made by Remko van Deijk.



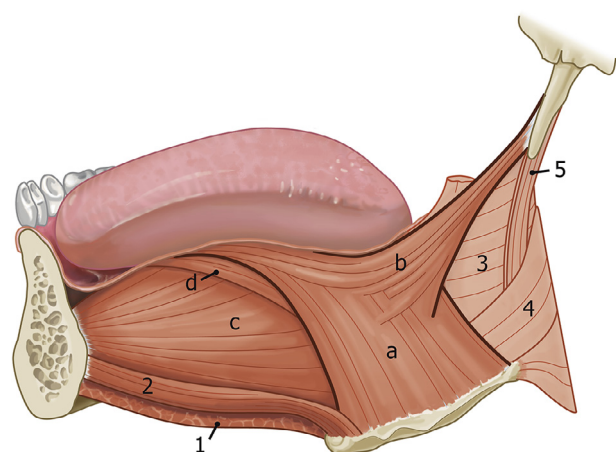
tonsils [19,20] (Fig. 2i). The palatopharyngeal muscles form the inner layer of the pharyngeal wall (anteriorly to the pharyngeal constrictors), and run further downward into the posterior border of the thyroid cartilage. Some of the muscle fibres are lost in the pharyngeal wall. The *stylopharyngeal muscle*, the third longitudinal pharyngeal muscle, is a long slender muscle that arises from the medial side of the base of the styloid process. It passes forward and downward along the side of the pharynx. Between the superior and middle pharyngeal constrictor, it runs into the inner layer of the pharyngeal wall and spreads out beneath the mucous membrane [19]. Some of its fibres are lost in the pharyngeal constrictors while others, joining the other two longitudinal muscles, run into the posterior border of the thyroid cartilage [19] (Fig. 2j).

#### FSUs involved in tongue base retraction

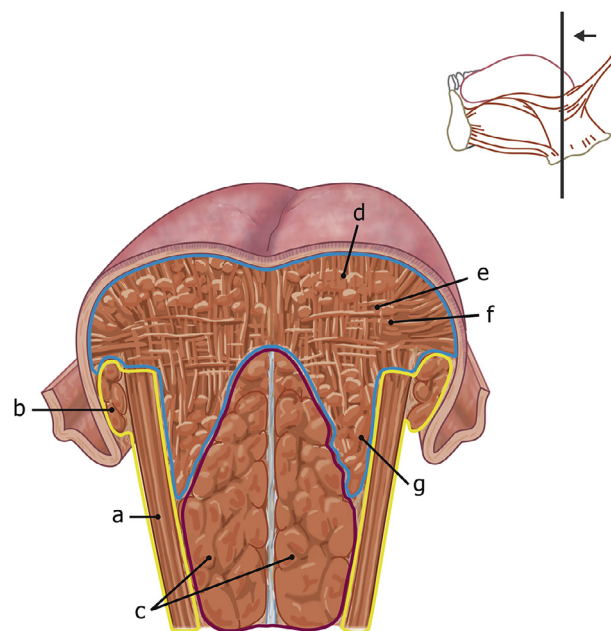
**Hyoglossus/styloglossus muscles complex (HSG)** consists of hyoglossus and styloglossus muscles. The *hyoglossus muscle* is a thin, quadrilateral muscle arising from the hyoid bone (the body and the greater cornu). It runs vertically upward and forward into the side of the tongue, ending at the aponeurosis linguae, an intrinsic layer of the strong connective tissue rigidly connected with the mucous membrane of the tongue [19,20] (Fig. 3a; Fig. 4a). The *styloglossus muscle* arises from the styloid process, near its apex. It passes downward and forward between the internal and external carotid arteries and divides at the side of the tongue near its dorsal surface. One part blends with the fibres of the intrinsic tongue muscles in front of the hyoglossus and the other, oblique, overlaps the hyoglossus and crosses with its fibres [19] (Fig. 3b; Fig. 4b). These two muscles co-operate with each other facilitating the tongue base retraction and thus, sufficient pressure building in the hypopharynx [28].

#### FSUs involved in tongue motion

**The genioglossus muscle (GGS)** is a flat triangular muscle located in the middle of the body of the tongue. Its apex corresponds with its origin (midline of the inner surface of the mandible), and its base corresponds with its insertion point into the



**Fig. 3.** a-b: muscles involved in tongue base retraction (TBR): a- hyoglossus muscle, b- styloglossus muscle (forming hyoglossus/styloglossus muscles complex (HSG), brown line). c-d: muscles involved in tongue motion (c- genioglossus muscle, d- inferior longitudinal intrinsic muscle). For better orientation and visualisation also illustrated: two floor of mouth muscles: 1- mylohyoid muscle, 2- geniohyoid muscle (only partly visible on Fig. 2c); pharyngeal constrictor muscles: 3- superior, 4- medius; 5- stylopharyngeal muscle. Illustration made by Remko van Deijk.



**Fig. 4.** Tongue musculature, coronal view, illustrating FSUs involved in tongue base retraction (TBR): hyoglossus/styloglossus muscles complex HSG (yellow line) and in tongue motion: genioglossus muscles GGS (red line), intrinsic tongue muscles ITM (blue line); a- hyoglossus muscle, b- styloglossus muscle, c- both genioglossus muscles separated by septum linguae, d- longitudinal superior intrinsic muscle, e- vertical intrinsic muscle, f- transverse intrinsic muscle, g- longitudinal inferior intrinsic muscle. Illustration made by Remko van Deijk.

tongue and hyoid bone. From the point of origin, it spreads out in a fan-like form [19] (Fig. 3c). The fibrous septum of the tongue (*septum linguae*), located in the midline, separates muscles of opposite sides [19]. Both muscles are considered as one functional unit (GGS) (Fig. 4c).

**The intrinsic tongue muscles (ITM, coral contour)** include four muscles on both sides (*superior longitudinal muscle, inferior longitudinal muscle, vertical muscle and transverse muscle*) arising from and ending in the body of the tongue [19]. They form a flexible, superficial muscular layer of the tongue, which inferiorly blends with the fibres of extrinsic muscles located more deeply. The main functions of their mutual co-operation is shortening and elongation, narrowing and thickening, flattening and broadening of the tongue, which allows flexible shape modification, crucial for proper and safe bolus preparation [19–21,42,43] (Fig. 3d; Fig. 4d–g). These muscles, together with the genioglossus muscles described above, support tongue motion during the oral preparatory phase.

#### **Discussion**

It is obvious that optimal prevention and management of radiation-induced dysphagia begins with a good understanding of the physiology of swallowing. There is a wide variety of dysphagia related end-points (subjective patient- and physician-rated scores, objective fibre-endoscopy and videofluoroscopy-based scores etc.) and a number of swallowing structures that may be injured during radiotherapy. This variety of end-points and number of structures make research into this problem, as well as a proper interpretation of results, very challenging. As the correlation between these different dimensions of swallowing problems is not always obvious, it is very likely that for every endpoint different structures may reveal the most important. Based on collected data and literature, we hypothesise that for aspiration (very often silent), beside the larynx itself, especially the

mechanism of hyolaryngeal elevation (and subsequently- involved structures) is the weakest link in the swallowing chain [17,44,45]. On the other hand, selected PROMS correlate with the dose to the tongue muscles and there is also enough data suggesting a profound role of the dose to pharyngeal constrictor muscles in developing diet alterations (i.e. RTOG physician-rated dysphagia) [16,46,47]. The relevance of dose to a certain structure is usually determined by its contribution to the best performing NTCP model for a particular endpoint. Having robust models (including the whole spectrum of swallowing structures as potential predictors) will support the selection of structures to spare. In the way, the prioritising of swallowing structures will depend on the prioritising of the endpoints for the individual patient. In this regard, the comprehension of swallowing physiology and anatomy is necessary for a more structured, hypothesis-driven approach to dysphagia. This is why the information presented here is highly relevant for radiation oncologists, treating patients with head and neck cancer.

To our knowledge, this is the first paper addressing SWAORs from an anatomical as well as a physiological perspective. Furthermore, the concept of Functional Swallowing Units (FSU) provides a theoretical basis for upcoming papers on radiation-induced dysphagia, focusing on clinical relevance of hyolaryngeal elevation and tongue function as well as for more advanced CT-based delineation guidelines for all FSUs (PART 2 of this series). Both papers (PART 1 and PART 2) are result of longer learning process, supported by prospectively collected data (including videofluoroscopy), pilot analyses, testing the hypothesis of relevance of defined FSUs, and encouraging preliminary results [16].

Previous authors have emphasised the importance of hyolaryngeal elevation (HLE) during the swallowing process. The theory of upper oesophageal sphincter opening, where the hyolaryngeal elevation plays a crucial role, was already established in the late eighties of 20th century [48,49]. Moreover, the role of the stylohyoid and posterior digastric complex, supporting the hyolaryngeal elevation, has been demonstrated [50]. Encouraged by these and their own findings, Pearson et al. conducted functional MRI studies and demonstrated that tongue base retraction (TBR) is facilitated by the hyoglossus and styloglossus muscles, and the hyolaryngeal elevation (HLE) by the floor of mouth and longitudinal pharyngeal muscles [24,27,28]. They also disagreed with current radiation practice (i.e. not considering these muscles as SWOARs) and they suggested that the variables representing structure-to-function relationship should be used for future IMRT studies (i.e. choosing HLE as the outcome variable representing the function of suprahyoid/longitudinal pharyngeal muscles) [27]. The functional approach of the present study corresponds strongly with Pearson's functional-anatomy-based theory of (post-radiation) swallowing disorders. The concept of Functional Swallowing Units, involved in HLE and TBR, furthermore covers all engaged muscles.

There is ample evidence to support the importance of HLE and TBR both in the swallowing process as well as in the pattern of radiation-induced dysphagia [4,32–37]. Despite this, in their pioneer paper on dysphagia/aspiration-related structures (DARS), Eisbruch et al. did not consider the suprahyoid and the tongue muscles relevant, based on the absence of anatomical changes in CT-scans [15]. However, the question arises as to whether this absence of CT-based structural abnormalities implies that their function remains unaffected. Several authors followed Eisbruch's approach and most published reports include only the pharyngeal constrictors and the larynx as SWOARs [46,51–54]. Therefore, limited data exist on the dose-effect relationship for HLE and TBR structures. In a pilot study, the analysis of our own prospectively collected data, showed that the dose to some components of aforementioned FSUs correlated significantly with subjective dysphagia outcomes, indicating that the dose to these structures may be at least as relevant as the dose to pharyngeal constrictors or the

larynx [16]. Meanwhile, results of two other retrospective studies revealed that floor of mouth and tongue muscles are indeed relevant for the development of radiation-induced dysphagia [17,25,45]. The authors concluded that, beside the dose to pharyngeal constrictors, the dose to non-target swallowing muscles should be monitored, due to unintended dose distributions and consequent beam path toxicities [17,55].

The results of these studies support the hypothesis that the dose to FSUs plays a significant role in radiation-induced dysphagia. Analysing the relationship between dose parameters to FSUs and functional components of swallowing (such as HLE and TBR) may provide additional insight into the development of radiation-induced dysphagia and therefore new opportunities for primary and secondary prevention. In this regard, it is crucial that during treatment planning, no relevant swallowing structures are unintentionally compromised. It is possible that some NTCP dysphagia models need to be reconsidered, as the dose to FSUs was previously not taken into account. Finally, (prophylactic) swallowing exercises could also be better targeted to specific muscle groups [18,28,38].

## Conclusion

An anatomy- and physiology-based concept of Functional Swallowing Units has been presented as the basis for a better understanding of radiation-induced dysphagia. Additional insight into this complex toxicity is crucial for further improvement of swallowing-sparing strategies. Moreover, it forms a solid, theoretical foundation for FSUs delineation guidelines (published separately as PART 2), supporting robust contouring, uniform data collection and the development of new swallowing sparing strategies.

## Conflict of interest statement

The authors declare no conflict of interest.

## References

- [1] Wopken K, Bijl HP, van der Schaaf A, et al. Development and validation of a prediction model for tube feeding dependence after curative (chemo-) radiation in head and neck cancer. *PLoS One* 2014;9:e94879.
- [2] Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;26:3770–6.
- [3] Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Leemans CR, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. *Radiother Oncol* 2009;90:189–95.
- [4] Smith RV, Kotz T, Beitler JJ, Wadler S. Long-term swallowing problems after organ preservation therapy with concomitant radiation therapy and intravenous hydroxyurea: initial results. *Arch Otolaryngol Head Neck Surg* 2000;126:384–9.
- [5] Nguyen NP, Frank C, Moltz CC, et al. Aspiration rate following chemoradiation for head and neck cancer: an underreported occurrence. *Radiother Oncol* 2006;80:302–6.
- [6] Murphy BA, Gilbert J. Dysphagia in head and neck cancer patients treated with radiation: assessment, sequelae, and rehabilitation. *Semin Radiat Oncol* 2009;19:35–42.
- [7] Nguyen NP, Moltz CC, Frank C, et al. Long-term aspiration following treatment for head and neck cancer. *Oncology* 2008;74:25–30.
- [8] Chen SW, Yang SN, Liang JA, Lin FJ. The outcome and prognostic factors in patients with aspiration pneumonia during concurrent chemoradiotherapy for head and neck cancer. *Eur J Cancer Care (Engl)* 2010;19:631–5.
- [9] Mortensen HR, Jensen K, Grau C. Aspiration pneumonia in patients treated with radiotherapy for head and neck cancer. *Acta Oncol* 2013;52:270–6.
- [10] Hunter KU, Lee OE, Lyden TH, et al. Aspiration pneumonia after chemointensity-modulated radiation therapy of oropharyngeal carcinoma and its clinical and dysphagia-related predictors. *Head Neck* 2014;36:120–5.
- [11] Kerr P, Myers CL, Butler J, Alessa M, Lambert P, Cooke AL. Prospective functional outcomes in sequential population based cohorts of stage III/IV oropharyngeal carcinoma patients treated with 3D conformal vs. intensity modulated radiotherapy. *J Otolaryngol Head Neck Surg* 2015;44. 17-015-0068-4.

- [12] Cilla S, Deodato F, Macchia G, et al. Volumetric modulated arc therapy (VMAT) and simultaneous integrated boost in head-and-neck cancer: is there a place for critical swallowing structures dose sparing? *Br J Radiol* 2016;89:20150764.
- [13] Franzese C, Fogliata A, Clerici E, et al. Toxicity profile and early clinical outcome for advanced head and neck cancer patients treated with simultaneous integrated boost and volumetric modulated arc therapy. *Radiat Oncol* 2015;10: 224–015-0535-0.
- [14] Christianen ME, Langendijk JA, Westerlaan HE, van de Water TA, Bijl HP. Delineation of organs at risk involved in swallowing for radiotherapy treatment planning. *Radiother Oncol* 2011;101:394–402.
- [15] Eisbruch A, Schwartz M, Rasch C, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? *Int J Radiat Oncol Biol Phys* 2004;60:1425–39.
- [16] Gawryszuk A, van der Laan HP, Langendijk JA. PD-0092: the dose to the larynx elevation and tongue retraction muscles has a large impact on post-radiation dysphagia. *Radiother Oncol* 2013;106:36.
- [17] MD Anderson Head and Neck Cancer Symptom Working Group. Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: Dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy. *Radiother Oncol* 2016;118:304–14.
- [18] Pearson Jr WG, Davidoff AA, Smith ZM, Adams DE, Langmore SE. Impaired swallowing mechanics of post radiation therapy head and neck cancer patients: A retrospective videofluoroscopic study. *World J Radiol* 2016;8: 192–9.
- [19] Gray H. Splanchnology. In: Gray H, editor. *Anatomy of the human body*. Philadelphia: Lea & Febiger; 1918. Bartleby.com Edition, New York, 2000.
- [20] Sokolowska-Pituchowa J. Muscles of the neck. In: Sokolowska-Pituchowa J, Krechowicki A, Kubik W, editors. *Human anatomy. Handbook for medical students*. Warsaw: Panstwowy Zakład Wydawnictw Lekarskich; 1983. p. 400–58.
- [21] Logemann JA. Evaluation and treatment of swallowing disorders. Austin: Pro-ed, An International Publisher. 1998;5-47:281–298.
- [22] Martin-Harris B, Brodsky MB, Michel Y, et al. MBS measurement tool for swallow impairment–MBSImp: establishing a standard. *Dysphagia* 2008;23:392–405.
- [23] Murray J. Manual of dysphagia assessment in adults. Dysphagia series. New York: Delmar Cengage Learning; 1999. p. 90–143.
- [24] Pearson Jr WG, Langmore SE, Zumwalt AC. Evaluating the structural properties of suprahyoid muscles and their potential for moving the hyoid. *Dysphagia* 2011;26:345–51.
- [25] Starmer HM, Quon H, Kumar R, et al. The effect of radiation dose on swallowing: Evaluation of aspiration and kinematics. *Dysphagia* 2015;30:430–7.
- [26] Pearson Jr WG, Taylor BK, Blair J, Martin-Harris B. Computational analysis of swallowing mechanics underlying impaired epiglottic inversion. *Laryngoscope* 2016;126:1854–8.
- [27] Pearson Jr WG, Hindson DF, Langmore SE, Zumwalt AC. Evaluating swallowing muscles essential for hyolaryngeal elevation by using muscle functional magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2013;85:735–40.
- [28] Gassert RB, Pearson Jr WG. Evaluating muscles underlying tongue base retraction in deglutition using muscular functional magnetic resonance imaging (mfMRI). *Magn Reson Imaging* 2016;34:204–8.
- [29] Jacob P, Kahrilas PJ, Logemann JA, Shah V, Ha T. Upper esophageal sphincter opening and modulation during swallowing. *Gastroenterology* 1989;97:1469–78.
- [30] Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. *Dysphagia* 1996;11:93–8.
- [31] Robbins J, Coyle J, Rosenbek J, Roecker E, Wood J. Differentiation of normal and abnormal airway protection during swallowing using the penetration-aspiration scale. *Dysphagia* 1999;14:228–32.
- [32] Lazarus CL. Effects of chemoradiotherapy on voice and swallowing. *Curr Opin Otolaryngol Head Neck Surg* 2009;17:172–8.
- [33] Lazarus CL, Logemann JA, Pauloski BR, et al. Swallowing disorders in head and neck cancer patients treated with radiotherapy and adjuvant chemotherapy. *Laryngoscope* 1996;106:1157–66.
- [34] Graner DE, Foote RL, Kasperbauer JL, et al. Swallow function in patients before and after intra-arterial chemoradiation. *Laryngoscope* 2003;113:573–9.
- [35] Agarwal J, Dutta D, Palwe V, et al. Prospective subjective evaluation of swallowing function and dietary pattern in head and neck cancers treated with concomitant chemo-radiation. *J Cancer Res Ther* 2010;6:15–21.
- [36] Rosenthal DI, Lewin JS, Eisbruch A. Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. *J Clin Oncol* 2006;24:2636–43.
- [37] Lee SY, Kim BH, Park YH. Analysis of dysphagia patterns using a modified barium swallowing test following treatment of head and neck cancer. *Yonsei Med J* 2015;56:1221–6.
- [38] Miloro KV, Pearson Jr WG, Langmore SE. Effortful pitch glide: a potential new exercise evaluated by dynamic MRI. *J Speech Lang Hear Res* 2014;57:1243–50.
- [39] Perie S, Laccourreye L, Flahault A, Hazebrucq V, Chaussade S, St Guily JL. Role of videofluoroscopy in assessment of pharyngeal function in oropharyngeal dysphagia: comparison with videofluoroscopy and manometry. *Laryngoscope* 1998;108:1712–6.
- [40] Herring MJ, Fehrenbach SW. Illustrated anatomy of the head and neck. 4th ed. St. Louis: Elsevier/Saunders; 2013.
- [41] Simkins CS. Functional anatomy of the eustachian tube. *Arch Otolaryngol Head Neck Surg* 1943;38:476–84.
- [42] Peponi E, Glanzmann C, Willi B, Huber G, Studer G. Dysphagia in head and neck cancer patients following intensity modulated radiotherapy (IMRT). *Radiat Oncol* 2011;6:1.
- [43] Queiroz MA, Hullner M, Kuhn F, et al. PET/MRI and PET/CT in follow-up of head and neck cancer patients. *Eur J Nucl Med Mol Imaging* 2014;41:1066–75.
- [44] Pearson Jr WG, Langmore SE, Yu LB, Zumwalt AC. Structural analysis of muscles elevating the hyolaryngeal complex. *Dysphagia* 2012;27:445–51.
- [45] Kumar R, Madanikia S, Starmer H, et al. Radiation dose to the floor of mouth muscles predicts swallowing complications following chemoradiation in oropharyngeal squamous cell carcinoma. *Oral Oncol* 2014;50:65–70.
- [46] Christianen ME, Schilstra C, Beetz I, et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. *Radiother Oncol* 2011.
- [47] Christianen ME, Verdonck-de Leeuw IM, Doornaert P, et al. Patterns of long-term swallowing dysfunction after definitive radiotherapy or chemoradiation. *Radiother Oncol* 2015;117:139–44.
- [48] Cook IJ, Dodds WJ, Dantas RO, et al. Opening mechanisms of the human upper esophageal sphincter. *Am J Physiol* 1989;257:G748–59.
- [49] Perlman AL, Palmer PM, McCulloch TM, Vandaele DJ. Electromyographic activity from human laryngeal, pharyngeal, and submental muscles during swallowing. *J Appl Physiol* 1985;1999(86):1663–9.
- [50] Kurt T, Gurgor N, Secil Y, Yildiz N, Ertekin C. Electrophysiologic identification and evaluation of stylohyoid and posterior digastric muscle complex. *J Electromyogr Kinesiol* 2006;16:58–65.
- [51] Eisbruch A, Kim HM, Feng FY, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. *Int J Radiat Oncol Biol Phys* 2011;81: e93–9.
- [52] Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys* 2007;68:1289–98.
- [53] van der Laan HP, Gawryszuk A, Christianen ME, et al. Swallowing-sparing intensity-modulated radiotherapy for head and neck cancer patients: treatment planning optimization and clinical introduction. *Radiother Oncol* 2013;107:282–7.
- [54] Anand AK, Chaudhary AR, Shukla A, et al. Favourable impact of intensity-modulated radiation therapy on chronic dysphagia in patients with head and neck cancer. *Br J Radiol* 2008;81:865–71.
- [55] Rosenthal DI, Chambers MS, Fuller CD, et al. Beam path toxicities to non-target structures during intensity-modulated radiation therapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2008;72:747–55.